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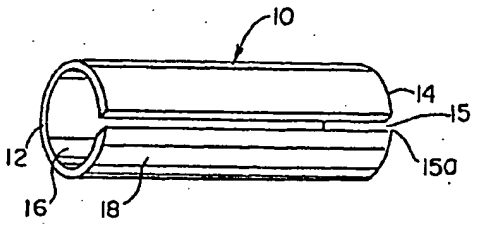
(54) Title: DRUG DELIVERY DEVICE FOR STENT

(57) Abstract

A device adapted for mounting on a stent, the device comprising a sheath being made of polymeric material that includes drugs such as pharmaceutical agent(s) or radioactive agent(s) for delivery to an implant site. The sheath includes a main body of a generally tubular shape, and may include mounting means for attaching same to the stent. The device may have a slit therein, and may comprise a helical coil, a cylinder or any other suitable shape or design which fits a particular stent. The sheath may include a coating or coatings thereon containing drugs, surgical adhesives or a combination thereof.



Description

titanium alloy. Decreased thrombogenicity is achievable by coating the outside of the coil with a non-thrombogenic material such as ULTI carbon.

Leeven et al., in U.S. Patent 4,820,298 describe a stent having a flexible tubular body made from a thermal plastic to the form of a helix. Polyester and polycarbonate copolymers are selected as particularly desirable materials.

Wolff et al., in U.S. Patent 4,830,003 describe a stent made from wires formed into a cylinder. The wires are made of a biocompatible metal. Biocompatible metals include 300 series stainless steels such as 316 LSS, as well as platinum and platinum-iridium alloys, cobalt-chromium alloys such as MP35N, and unalloyed titanium.

Wiktor in U.S. Patent 4,886,062 describes a stent made from low memory metal such as a copper alloy, titanium, or gold. The stent is preformed into a two-dimensional zig-zag form creating a flat expandable band.

Gianturco in U.S. Patent 4,907,336 describes a wire stent having a cylindrical shape that results from an expandable serpentine configuration. Malleable materials of construction are preferably included from the group of annealed stainless steels, tungsten and platinum.

Goldberg et al, in Canadian Application 2,025,626, describes a bio-degradable infusion stent used to treat ureteral obstructions. The application describes an extruded material of construction made of epsilon-caprolactone (15-25% w/w of terpolymer composition); glycoside (5-50% w/w) and L(-)lactide (45-85% w/w). This material was described as having a minimum tensile strength of at least 500 pounds per square inch, preferably 650 psi; elongation of greater than 10%, preferably greater than 100%; and Shore A hardness equal to 50-100%, preferably 75-95%. The Goldberg et al patent application describes a method for incorporating radiopaque materials such as barium sulfate into the polymer in amounts ranging from 5-30%. The mechanism of biodegradation is described as hydrolysis resulting in degradable products excreted in urine or reabsorbed into tissues. The duration of functional life of the stent is estimated at about 3-7 weeks.

Wilcoff in U.S. Patent 4,990,155 describes a plastic stent having an inherently expandable coil conformation. The "inherency" results from an elastic memory conferred by electron beam radiation imparting cross-linkages that provide an inherent tendency to return to a given diameter after any distortion. Materials of construction

restenosis. The torn wall or flap usually is the source of the blockage. When the wall is torn, a flap of tissue is created, which falls into the passage and blocks it. It is then necessary to perform another procedure to remove the blockage and generally, another stent is needed to open the vessel or other passage. Metal stents are known to cause 10% to 30% or more restenosis in application.

Therefore, it desirable to utilize a stent which reduces the chances of a damaged vessel wall or body passage which leads to further problems and further necessary procedures. However, current stents are not designed to reduce the occurrence of cutting of vascular passages or the like.

U.S. Patent Application No. 09/072,944, incorporated herein by reference, is directed to a stent having at least one smooth end. The stent may include a coating or coatings on one or both end portions to provide a smooth finish to reduce possible damage to body passages when the stent is deployed and delivered. The stent may also contain drugs or surgical adhesives or a combination thereof in or on the coated portion of the stent. The stent may also be of the type where the materials of the stent may be treated to have a smooth flexible end or ends. The stent may also be of a configuration such that at least one end is more flexible than the middle portion of the stent.

U.S. Patent Application No. 08/874,190, incorporated herein by reference, discloses a polymeric layered stent characterized in that it includes a multilayered material comprised of an inner polymer layer and an overlying outer polymer layer. The self-expanding or balloon expandable stent disclosed therein is provided in two forms, one including inner and outer polymeric layers, and another comprising a prior art stent provided with polymeric layer(s) coated thereon.

While U.S. Applications 09/072,944 and 08/874,190 are directed in part to this need, there still exists a need for a means for delivering drugs or biologically active agents which assist in preventing restenosis, which can be easily mounted on an existing stent prior to implantation.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention is to provide a polymeric device adapted for mounting onto a stent. The device of polymeric material may comprise a sheath or sleeve that is cylindrical, a helical coil, or any other suitable shape or design which fits a particular stent. The stent may be metallic or non-metallic, or alternatively a

Figure 10 is a fragementary perspective view as in Figure 9 showing the stent and sheath after expansion of the stent; and

Figure 11 is a fragementary side elevational view with parts broken away of the stent with the sheath of the present invention in an implanted site.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is a polymeric device adapted for mounting onto a stent. Referring to Figures 1-4, the device may be a sheath as shown generally at 10. Sheath 10 has a proximal end 12, a distal end 14, an interior surface 16 and an exterior surface 18.

As shown at Figures 2a, 2b and 3, sheath 10 may have a slit 15 therein extending from proximal end 12 to distal end 14. As shown at Figure 2a, slit 15 is a longitudinal slit 15a. Figure 2b shows the same sheath in a compressed configuration it may take on prior to being mounted on a stent. Alternatively, slit 15 may be a helical slit 15b, as shown at Figure 3.

Referring to Figure 4, sheath 10 may be provided with perforations 17 therethrough. In addition, sheath 10 may comprise multiple layers, for example as shown in cross section at Figure 5 having two layers. Alternatively, sheath 10 may comprise a plurality of layers. Referring to Figures 6-7, sheath 10 may be shaped like a spring, which spring may optionally be formed from a tubular member, as exemplified by the cross section at Figure 7.

Referring now to Figures 8-10, a sheath comprising a helical coil is shown. Figure 8 is a perspective view of sheath 10. At Figure 9, a partial section view of sheath 10 mounted on a stent 20 is shown prior to implantation and expansion. Stent 20 includes a generally tubular main body 21, a proximal end 22 (not shown in this view), a distal end 24 (not shown in this view), an interior surface 26 and an exterior surface 28. Prior to implantation, sheath 10 is mounted on stent 20 such that the exterior surface 28 of main body 21 faces the interior surface 16 of sheath 10.

In use, sheath 10 is placed on the outer surface 24 of stent 20 prior to implantation thereof. Sheath 10 may be held on stent 20 by any suitable means including compressive force, glue, a protective sheath, socks or the like.

The compressive force may be supplied by the sheath itself, the stent or both. The glue is preferably a biocompatible glue such as fibrin, collagen or gelatin. Any

sheath 10 faces an inner surface wall 34 of the vessel 32. Stent 20 provides mechanical support to tubular vessel 32 in a living being. The stent strengthens the area of vessel 32 in which it is implanted. Sheath 10 releases a pharmaceutical agent or radioactive agent into lumen 30 of tubular vessel 32. The rate of release may vary.

The present invention may be used with any stent. Such a stent may range from 1 millimeter in diameter to 50 millimeters in diameter and from 1 millimeter in length to 50 millimeters in length. The size of the stent is dictated by the lumen of the vessel to which the stent is placed. Tubular main body 21 suitably has a length of up to approximately 5 centimeters.

Sheath 10 may be of any size suitable for use with a stent being implanted.

Many suitable materials may be used to form the sheath 10 of the present invention. For example, hydrophilic polymers, copolymers (block or graft) or their cross-linked versions (e.g. hydrogels), may be used, the polymers including poly(hydroxyethyl methacrylate) and derivatives; poly(vinyl alcohol); polyethylene oxide; poly(propylene oxide); polyacrylamides; polyacrylic acid; polymethacrylic acid; poly(N-vinyl-2-pyrollidone); hydrophilic polyurethanes; poly(amino acid); water soluble cellulosic polymers (sodium carboxymethyl cellulose, hydroxyethyl cellulose, for example); collagens; carrageenan; alginate; starch; dextrin; and gelatins.

The device of the present invention may be made of biodegradable polymers including poly(lactide); poly(glycolide); polydioxanone(PDS); polycaprolactone; polyhydroxybutyrate(PHBT); poly(phosphazene); poly(phosphate ester); poly(lactide-co-glycolide); poly(glycolide-co-trimethylene carbonate); poly(glycolide-co-caprolactone); polyanhydrides; collagen or other connective proteins or natural materials, hyaluronic acid, adhesive proteins, co-polymers of these materials as well as composites or combinations thereof and combinations of other biodegradable polymers.

In addition, the device of the present invention may be made of biodegradable materials that are also biocompatible. By biodegradable is meant that a material will undergo breakdown or decomposition into harmless compounds as part of a normal biological process. The device may also include bioactive agents which permit endothelial cells to grow on the device and the stent. It is believed that the endothelial cell growth will encapsulate particles of the stent during biodegradation that would otherwise come loose and form emboli in the blood stream.

solutions, dispersing into the biodegradable polymer during the formation of the sheath, or coating onto an already formed sheath.

Where the sheath has a film added thereto, drugs can be incorporated into the film by methods such as melting or solvation. Alternatively, biologically active agents are incorporated into the film layer by entrapment between such layer and the surface of biodegradable material sandwiched together, thereby further promoting release of the drugs or agents in a controllable manner.

The drugs or other biologically active materials incorporated into the sheath of the present invention perform a variety of functions. The functions include but are not limited to an anti-clotting or anti-platelet function and preventing smooth muscle cell growth on the inner surface of the vessel to reduce the chance of in-stent restenosis. The drugs include but are not limited to drugs that inhibit or control the formation of thrombus or thrombolytics such as heparin or heparin fragments, aspirin, coumadin, tissue plasminogen activator (TPA), urokinase, hirudin, and streptokinase, antiproliferatives (methotrexate, cisplatin, 5-fluorouracil, Taxol, Adriamycin, and the like) antioxidants (ascorbic acid, carotene, B, vitamin E, and the like), antimetabolites, thromboxane inhibitors, non-steroidal and steroidal antiinflammatory drugs, Beta and Calcium channel blockers, genetic materials including DNA and RNA fragments, and complete expression genes, carbohydrates, and proteins including but not limited to antibodies (monoclonal and polyclonal) lymphokines and growth factors, prostaglandins, and leukotrienes. The sheath material may also incorporate bioactive materials such as fibronectin, laminin, elastin, collagen, and intergrins. Fibronectin, for example, promotes adherence of the sheath to the tissue of the vessel 32.

In one specific example of a biodegradable material incorporating drugs, a poly-L-lactide having an intrinsic viscosity of 2.3 dl/g is used to form monofilament fibers using a spin or melt spinning process. Five percent aspirin or 5% heparin was incorporated into the melt of the poly-L-lactide prior to fiber formation. The fibers formed had a diameter of approximately 0.5 millimeters. The monofilaments were then stretched under temperatures ranging from 50° C to 200° C to orient the fiber. The temperature employed depends upon the kind of material used to make the fiber. The final diameter of the oriented fiber falls within a range of 0.1 to 0.3 millimeters. Similar processing was used to incorporate 5% aspirin or 5% heparin into poly-L-lactide and polyglycolide.

Another way is to form a sleeve from a gel-like material without a drug, or to coat or laminate a polymeric sleeve with a gel-like material without the drug. The sleeve is made, and then sterilized. Due to the gel-like nature, the sleeve can then be inserted into a drug solution. The drug will be absorbed into/onto the gel.

The resulting drug-carrying sleeve can then be mounted to a stent and delivered into the body. The drug will then be released.

In one embodiment of the invention, the sleeve may be made of polyethylene oxide containing Taxol or coated with such a material. Other materials that may be used are copolymers such as PGA/PLA, PEO/PLA or the like containing a drug such as Taxol or heparin.

Preferred gel- like materials for use as a drug delivery sleeve or coating for a stent when drug delivery is desired are polyethylene oxide, polyvinyl pyrollidone, polyacrylates, and their blends or copolymers or lightly cross linked forms. Polyethylene glycol block copolymer with polylactides or other polyesters are examples. Hydrophilic polyurethane, poly(maleic anhydride-alt-ethylene) and their derivatives are examples. Other materials are polysaccharides and their derivatives. There are also sodium alginate, karaya gum, gelatin, guar gum, agar, algin carrageenans, pectin, locust bean gums, xanthan, starch-based gums, hydroxy alkyl and ethyl ethers of cellulose, sodium carboxymethyl cellulose. Some of the materials will be heated, then cooled, then a gel is formed. Some of the above are food gels. Some of them are bioadhesives.

Any drugs may be used, singly or in combination. For example, the drugs can be an anticoagulant, e.g. aspirin, ticlopidine, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, antibodies, urokinase, prostaglandin inhibitors, platelet inhibitors, or antiplatelet peptide. The drug can be an inhibitor of vascular cell growth, DNA, RNA, cholesterol-lowering agents, vasodilating agents. The drug can be any drug such as Taxol, 5-fluorouracil, Beta-Estradiol, Tranilast, Trapidil, Probucol, Angiopeptin or any combination of them.

Since there are many drugs and many polymers, the sleeve can have multiple layers of different polymers with the same or different drugs. For example, the sleeve can have two layers of the same polymer with one layer with drug and another layer without drugs. The sleeve may have two layers of the same polymer with two different drugs as another example.

gelatin-resorcinol-formol (GRF) glue: formed from gelatin, resorcinol and water in the presence of formaldehyde, glutaraldehyde and heat (45°C);

mussel adhesive protein, prolamine gel and transforming growth factor beta(TGF-B);

polyacrylic acid, modified hydrocellulose, hydroxypropylmethyl cellulose, hydroxypropylcellulose, carboxymethyl cellulose, sodium alginate, gelatin, pectin, polyvinylpylindone, polyethylene glycol, aldehyde relative multifunctional chemicals, polyallylsaccharose, and polypeptides.

Suitable materials for the device of the present invention and suitable drugs to be delivered thereby are also set forth in U.S. Application No. 08/874,190.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

The above Examples and disclosure are intended to be illustrative and not exhaustive. These examples and description will suggest many variations and alternatives to one of ordinary skill in this art. All these alternatives and variations are intended to be included within the scope of the attached claims. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims attached hereto.

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WHAT IS CLAIMED IS:

What is claimed is:

1. An implantable intraluminal apparatus comprising in combination:

an expandable intraluminal stent comprising a main body portion having a first end portion, a second end portion, a middle portion, an exterior surface and an interior flow passage defined therethrough; and

a sheath constructed and arranged for mounting on the stent for delivery of drugs to an implanted site, said sheath comprising a biocompatible polymeric material and a drug carried thereby.

2. The apparatus of claim 1 wherein the sheath comprises polyurethane.

3. The apparatus of claim 1 wherein the sheath comprises polytetrafluoroethylene.

4. The apparatus of claim 1 wherein the sheath comprises a gel-like material.

5. The apparatus of claim 1 wherein the sheath comprises a cellulose polymer.

6. The apparatus of claim 1 wherein the sheath comprises a biodegradable polymer.

7. The apparatus of claim 1 wherein the sheath comprises poly(N-vinyl-2-pyrollidone).

8. The apparatus of claim 1 wherein the sheath comprises polyethylene oxide.

9. The apparatus of claim 1 wherein the drug is selected from the group consisting of pharmaceutical agents, radioactive agents, bioactive agents and combinations thereof.

11. The apparatus of claim 1 wherein the drug is selected from the group consisting of TAXOL, vascular endothelial growth factor, heparin, 5-fluorouracil, beta-estradiol, tranilast, trapidil, probucol, and angiopeptin.

12. The apparatus of claim 1 wherein the sheath is cylindrical.

13. The apparatus of claim 1 wherein the sheath further comprises a proximal end, a distal end and a slit extending from the proximal end to the distal end.

14. The apparatus of claim 13 wherein the slit is a longitudinal slit.

15. The apparatus of claim 13 wherein the slit is helical.

16. The apparatus of claim 1 wherein the sheath is a helical coil.

17. The apparatus of claim 1 wherein the sheath comprises a plurality of layers.

18. The apparatus of claim 17 wherein the plurality of layers is comprised of the same material.

19. The apparatus of claim 17 wherein the plurality of layers is comprised of different materials.

37. A drug delivery sheath for delivering drugs within the body, the sheath constructed and arranged for being associated with a stent for delivery of drugs to an implanted site, said sheath comprising a biocompatible polymeric material and a drug carried thereby.

38. A sheath constructed and arranged for being introduced within the body for delivery of drugs to an implanted site, said sheath comprising a biocompatible polymeric material and a drug carried thereby.

Fig. 8

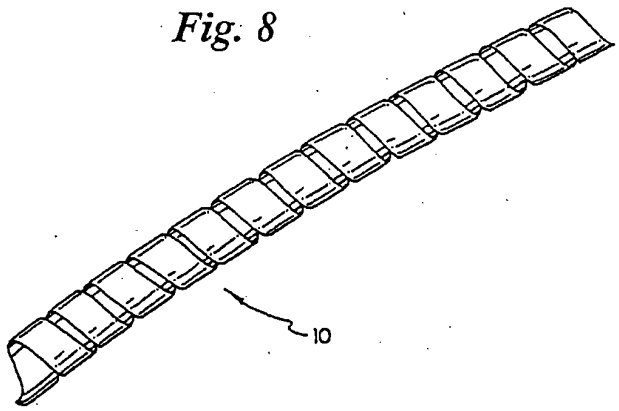
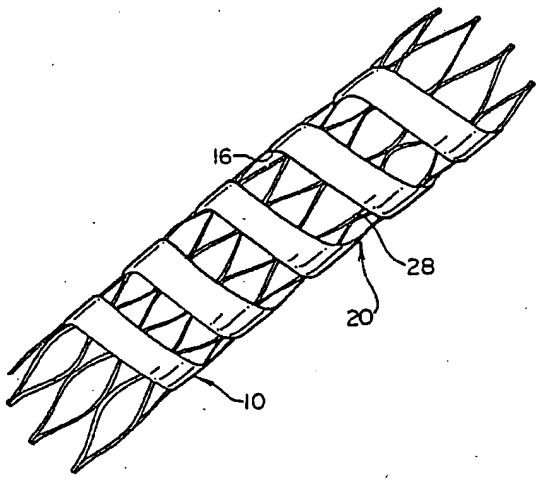


Fig. 10



INTERNATIONAL SEARCH REPORT

Intl. Ional Application No
PCT/US 99/19697

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/08 A61L31/16 A61L31/18 A61K51/12 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 716 836 A (ADVANCED CARDIOVASCULAR SYSTEM) 19 June 1996 (1996-06-19) claims; figures	1-38
X	EP 0 712 615 A (ADVANCED CARDIOVASCULAR SYSTEM) 22 May 1996 (1996-05-22) claims	1-38
X	EP 0 604 022 A (ADVANCED CARDIOVASCULAR SYSTEM) 29 June 1994 (1994-06-29) claims	1,6,9, 11, 17-22, 26,29-38
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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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